



Guillain-Barré and Alpha-gal Syndromes: Saccharides-induced Immune Responses

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Abstract

The molecular interactions between hosts, vectors and pathogens drive the etiology of infectious diseases. At first sight, the Guillain-Barré and Alpha-Gal syndromes have quite different etiologies but, as proposed here, a closer look into the immune response to galactose-containing oligosaccharide structures that characterizes these two diseases reveals striking commonalities. In this Opinion paper, we address the main molecular drivers of two apparently unrelated diseases, and how the characterization of the immune response and immunological tolerance would advance the control and prevention of these diseases.

Guillain-Barré syndrome (GBS) is an immune-mediated peripheral neuropathy, with an annual incidence of approximately 1–2 cases per 100,000 persons.^{1–3} The most common symptom of GBS is a rapidly evolving, ascending weakness, with mild sensory loss and hyporeflexia or areflexia progressing to a nadir over up to 4 weeks.^{2,3} GBS is considered to be an autoimmune disease with involvement of both cellular and humoral immune responses,² but about a quarter of the patients with GBS have suffered a recent bacterial or viral infection, and axonal forms of the disease are especially common in these patients.^{2,4–9} Pathogens such as *Campylobacter jejuni*, *Haemophilus* bacteria and Cytomegalovirus have been shown to have oligosaccharide structures [Gal beta 1-3 GalNAc beta 1-4 (NeuAc alpha 2-3) Gal beta] in their lipopolysaccharide coat responsible for the molecular mimicry that triggers GBS.^{2,5,7,10–13} In addition, different types of viral diseases, such as hepatitis caused by hepatitis C virus, acquired immune deficiency syndrome caused by the human immunodeficiency virus and disease caused by the mosquito-borne Zika virus, have been related to GBS.^{8,9} Additionally, rare cases of GBS have been reported after treatment with inactivated influenza vaccine.¹⁴ Recent results have shown that infection with these pathogens leads to anti-GM1 pen-

tasaccharide beta-Gal-(1-3)-beta-GalNAc-(1-4)-[alpha-Neu5Ac-(2-3)]-beta-Gal-(1-4)-beta-Glc antibody production, which cross-reacts with gangliosides and other glycolipids, leading to myelin destruction by complement activation or by antibodies targeting macrophages via the Fc receptor and leading to both demyelination and nerve conduction failure.^{2,4,15}

Alpha-Gal syndrome (AGS) is a tick-induced allergy triggered by IgE antibody response against the carbohydrate Gal α 1-3Gal β 1-(3)4GlcNAc-R (α -Gal), which is present in glycoproteins from tick saliva and tissues of noncatarrhine mammals.^{16,17} AGS is characterized by delayed anaphylaxis to red meat consumption and certain drugs, such as cetuximab, and immediate anaphylaxis to tick bites, and is becoming a global problem with increasing prevalence in all continents and with the involvement of several tick species.^{16–20} Humans do not produce the carbohydrate α -Gal (Gal α 1-3Gal β 1-(3)4GlcNAc-R),²¹ and the not yet fully understood immune response induced by tick bites that includes anti- α -Gal IgE antibodies break the oral tolerance to food allergens, resulting in a gut-related but not lung-related allergy.^{16,20} The *GGTA1* gene encoding for the α 1,3-galactosyltransferase enzyme that synthesizes α -Gal in mammals was inactivated in humans, apes and Old World monkeys approximately 28 million years ago.²¹ This resulted in an almost unique capacity of these animals to produce high levels of anti- α -Gal antibodies. Several pathogens, such as *Leishmania*, *Trypanosoma*, *Plasmodium* and *Mycobacterium*, have been found to produce α -Gal on their surface, and infection with some of these pathogens induces an anti- α -Gal response.^{22,23} Anti- α -Gal antibodies can also be produced in response to bacterial microbiota,²¹ and they constitute the most abundant antibody in humans, representing about 1% of total immunoglobulins.²¹

Anti- α -Gal IgG and IgM antibodies induced by bacterial microbiota were shown to control malaria transmission by complement-mediated lysis.²² The proposed mechanisms triggering AGS

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Abbreviations: α -Gal, Gal α 1-3Gal β 1-(3)4GlcNAc-R; AGS, alpha-Gal syndrome; GBS, Guillain-Barré syndrome.

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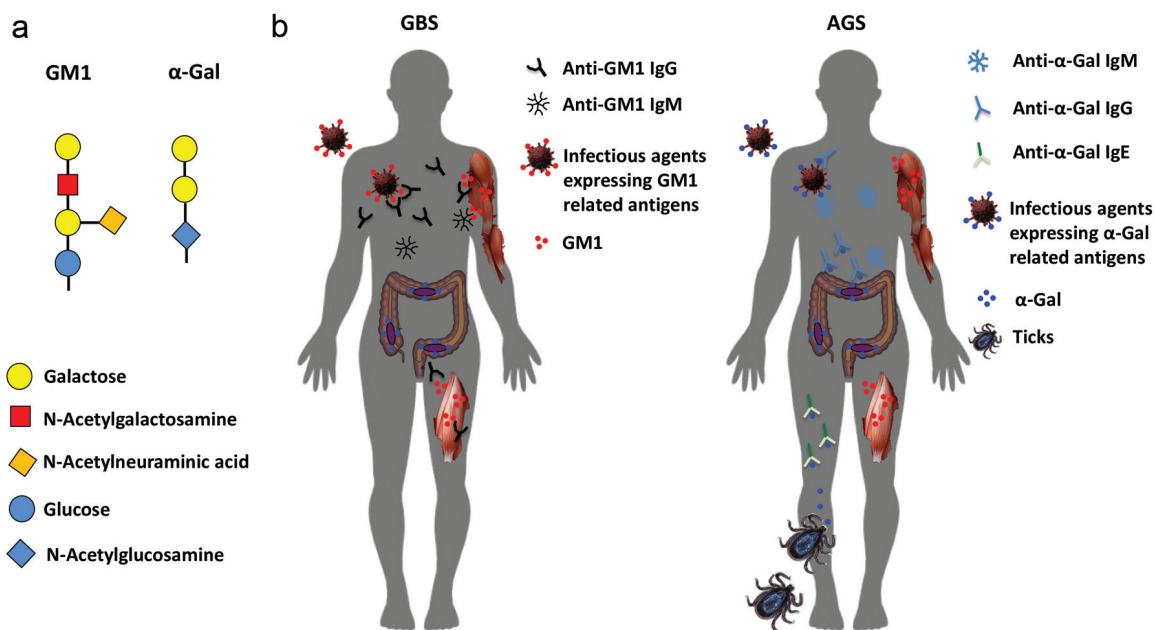


Fig. 1. Immunological similarities between GBS and AGS. (a) Both GBS and AGS are associated to galactose-containing antigens (GM1 and α-Gal), in which galactose plays an important role as an antigenic determinant. The chemical structures of GM1 and α-Gal are shown. (b) Interplay between infectious agents producing GM1 or α-Gal-related antigens and GM1 present in human tissues and α-Gal molecules present on the bacterial microbiota. In case of AGS, the α-Gal is found in human gut and associated to microbiota bacteria and food (*i.e.* red meat). Immune tolerance is lost in both diseases. In GBS, the presence of GM1 on pathogens break the tolerance against this molecule produced in myelinated axons that are associated to motor and sensory nerves. In AGS, pathogens and microbiota induce high levels of anti-α-Gal IgM and IgG but after tick bites, anti-α-Gal IgE is produced. This process breaks the oral tolerance to food antigens containing α-Gal and results in anaphylactic reaction to red meat. α-Gal, Galα1-3Galβ1-(3)4GlcNAc-R; AGS, alpha-Gal syndrome; GBS, Guillain-Barré syndrome.

involve Toll-like receptor-mediated responses in both Th1 and Th2 cells, with a role for basophils in this process.¹⁶ Therefore, *GGT1* gene inactivation might have occurred in response to the selection pressure exerted by pathogens detrimental to primates that produce α-Gal.²¹ Consequently, the capacity of the human immune system to respond to pathogens producing α-Gal evolved with the tradeoff of AGS.^{17,24}

These results suggested that both GBS and AGS are related to infectious diseases and driven by immune response to galactose-containing oligosaccharide structures. Humans produce GM1 and the anti-GM1 antibodies induced by pathogen infection break the tolerance to the self-antigen GM1, leading to myelin destruction and GBS. However, humans do not produce α-Gal and anti-α-Gal IgE antibodies induced by tick bites result in anaphylactic reaction to the consumption of red meat containing this carbohydrate and leading to the AGS. Interestingly, both diseases overcome the immune tolerance 'easily', a mechanism otherwise known to be quite robust for other antigens, such as cancer-related antigens.²⁵ However, differences between the two diseases are also important to consider for the development of proper interventions.²⁶

The carbohydrate epitopes involved in GBS are very complex, including a range of gangliosides, such as GM2, GM1, GM1b, GD1a, GalNAc-Gd1a and GQ1b, that beside galactose involve other monosaccharides, including NeuNAc (5-N-acetylneuraminic acid) and GalNAc (2-N-acetyl-galactosamine). The NeuNAc is found in most epitopes of GBS, playing the most important role in the immunochemistry of GBS carbohydrate epitopes. However, the galactosyl oligosaccharide residue plays an essential role in AGS. Pathomechanistically, GBS is the result of the body's adap-

tive immune response to foreign antigens, which have structures similar to human gangliosides that generate antibodies accidentally recognizing human gangliosides and resulting in autoimmune reactions. On the other hand, AGS is an allergic reaction triggered by tick bites and after eating red meat containing the α-Gal trisaccharide, which is a hyper-reaction of human immune systems to foreign antigens.¹⁶

What we can learn from these findings? Besides differences in the carbohydrate epitopes playing the main role in GBS and AGS and other pathomechanistic differences, the immunological basis of GBS and AGS have some similarities (Fig. 1). Trying to understand how immunity is regulated in response to galactose-containing oligosaccharides and other carbohydrate structures produced by pathogens and ticks that result in GBS or AGS is essential to prevent these diseases.^{15–17} Recent results from our group showed that application of the latest postgenomic or omics technologies would facilitate the characterization of the immune response in both GBS and AGS, with the possible identification of target molecules for diagnostics, treatment and prevention of these diseases.^{27–30}

In summary, deciphering the immune-mediated mechanisms involved in GBS and AGS would lead to new diagnostic, treatment and prevention/control interventions for these diseases, and have possible implications for the control of major infectious diseases.³¹

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Conflict of interest

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Study conception and design (JF, ACC); acquisition of data (IP, MC, LMH, MV, ACC, JF); analysis and interpretation of data (JF, ACC, MV); drafting of the manuscript (JF, MV); critical revision of the manuscript for important intellectual content (JF, ACC, MV); administrative, technical, or material support, and study supervision (JF, MV).

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